

**UNCLASSIFIED**

**AD 407 905**

---

**DEFENSE DOCUMENTATION CENTER**

**FOR**

**SCIENTIFIC AND TECHNICAL INFORMATION**

**CAMERON STATION, ALEXANDRIA, VIRGINIA**

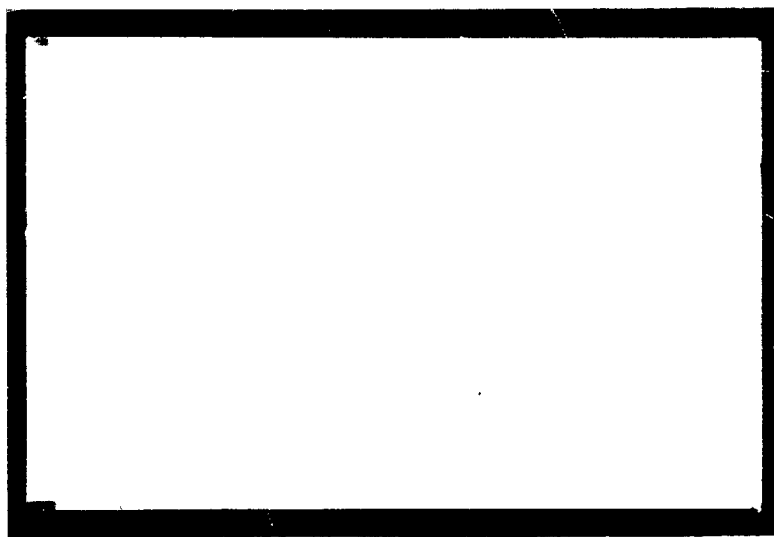


**UNCLASSIFIED**

NOTICE: When government or other drawings, specifications or other data are used for any purpose other than in connection with a definitely related government procurement operation, the U. S. Government thereby incurs no responsibility, nor any obligation whatsoever; and the fact that the Government may have formulated, furnished, or in any way supplied the said drawings, specifications, or other data is not to be regarded by implication or otherwise as in any manner licensing the holder or any other person or corporation, or conveying any rights or permission to manufacture, use or sell any patented invention that may in any way be related thereto.

CATALOGED BY DDC  
AS AD NO. 407905

407 905



63-4-2  
THE UNIVERSITY  
OF WISCONSIN  
*madison, wisconsin*



DDC  
RECEIVED  
JUN 14 1963  
TISIA D

MATHEMATICS RESEARCH CENTER

UNITED STATES A



MATHEMATICS RESEARCH CENTER, UNITED STATES ARMY  
THE UNIVERSITY OF WISCONSIN

Contract No.: DA-11-022-ORD-2059

A SEMI-MARKOV MODEL FOR  
CLINICAL TRIALS

George H. Weiss and Marvin Zelen

MRC Technical Summary Report #396  
April 1963

Madison, Wisconsin

## ABSTRACT

This paper applies the theory of Semi-Markov Processes to the construction of a stochastic model for interpreting data obtained from clinical trials. The model characterizes the patient as being in one of a finite number of states at any given time with an arbitrary probability distribution to describe the length of stay in a state. Transitions between states are assumed to be chosen according to a stationary finite Markov chain.

Other attempts have been made to develop stochastic models of clinical trials. However, these have all been essentially Markovian with constant transition probabilities which implies that the distribution of time spent during a visit to a state is exponential (or geometric for discrete Markov chains). Markov models need also to assume that the transitions in the state of a patient depend only on absolute time whereas the Semi-Markov model assumes that transitions depend on time relative to a patient. Thus the models are applicable to degenerative diseases (cancer, acute leukemia), while Markov models with time dependent transition probabilities are applicable to colds and epidemic diseases. In this paper the Laplace transforms are obtained for (i) probability of being in a state at time  $t$ , (ii) probability distribution to reach absorption state and (iii) the probability distribution of the first passage times to go from initial states to transient or absorbing states, transient to transient, and transient to absorbing. The model is applied to a clinical study of Acute Leukemia which have been treated with methotrexate and 6-mercaptopurine. The agreement of the data and the model is very good.

# A SEMI-MARKOV MODEL FOR CLINICAL TRIALS<sup>1</sup>

George H. Weiss<sup>2</sup> and Marvin Zelen<sup>3</sup>

## 1. Introduction

There are many diseases which can be characterized by the patient being in one of a finite number of states such that the sojourn time within a state is a random variable. For example, many clinical trials can be described as a course of treatment given to a patient who is in a state of illness or relapse, in the hope that the therapy will ultimately cure the patient or bring him into some degree of remission. During the course of the treatment the patient may be in remission and relapse states several times. When evaluating such courses of therapy in clinical trials it is important to be able to discuss various statistical characteristics of the therapy; i. e. , proportion cured or reaching a remission state, time to reach a given state for the first time, the first passage time to cure or death, the probability of being cured or reaching remission as a function of the duration of therapy, etc.

As a possibly more concrete motivation for the theory which follows, we mention the problem which stimulated our work. At the present time acute leukemia cannot be cured by any known therapy. It is known, however, that

---

<sup>1</sup> Sponsored in part by the Mathematics Research Center, U.S. Army, Madison, Wisconsin, under Contract No. DA-11-022-ORD-2059 and in part by Contract NONR 595(17).

<sup>2</sup> Institute of Fluid Dynamics and Applied Mathematics, University of Maryland and National Bureau of Standards.

<sup>3</sup> Mathematics Research Center, U.S. Army.

certain drugs can prolong a patient's life, or the period of relative freedom from symptoms characteristic of the disease. Currently a large-scale clinical program is underway, sponsored by the National Institutes of Health, to test the efficacy of many chemical agents on the course of the disease, with the object of being able to prolong life, if indeed it is not possible to discover an absolute cure. Hence, it is necessary to have idealized models which can be used as a framework for the analysis of the data. Perhaps the most important use of a model is as a guide in deciding the types of data to be taken during the course of a series of clinical trials. It is the purpose of this paper to discuss a general stochastic model for the description of the course of chronic diseases and the outcome of clinical trials. Our model is based on the theory of semi-Markov processes, (c.f. Pyke [1], [2]).

## 2. Earlier Models

Several studies have appeared in the literature with the same object as the present paper. However these earlier works treat the model as a strictly Markov process. The first of these, by Fix and Neyman, [3], discusses a four state continuous Markov process for the treatment of data on cancer patients. The four states were:

1. Under treatment
2. Dead following treatment or operative death
3. Alive, not under treatment for cancer, and  
remaining under observation.

4. Lost after apparent recovery, either through death not due to cancer or through difficulties of tracing the patient.

The equations characterizing Fix and Neyman's model are

$$\frac{dP}{dt} = -AP \quad (2.1)$$

where  $P$  is the vector of state probabilities, and  $A$  is a constant matrix. A formal solution to (2.1) can always be written  $P(t) = \exp(-At) P(0)$ , hence the probability of being in any one state at time  $t$  can always be written as a weighted sum of negative exponential terms. Fix and Neyman also discuss estimation procedures for fitting the parameters in their model.

Marshall and Goldhamer, [4], presented several discrete Markov chain models as a framework for the handling of data in connection with the epidemiology of mental disease. Their object was to characterize the age distributions of the mentally ill population. The states which figured in their analysis were the following:

1. Alive, sane
2. Alive, insane (mild) unhospitalized
3. Alive, insane (severe) unhospitalized
4. Insane, hospitalized
5. Dead, outside of mental institution.

The authors give a long discussion of their data and estimation procedures. Since their model supposes as the underlying descriptive equations



4. Lost after apparent recovery, either through death not due to cancer or through difficulties of tracing the patient.

The equations characterizing Fix and Neyman's model are

$$\frac{dP}{dt} = -AP \quad (2.1)$$

where  $P$  is the vector of state probabilities, and  $A$  is a constant matrix. A formal solution to (2.1) can always be written  $P(t) = \exp(-At) P(0)$ , hence the probability of being in any one state at time  $t$  can always be written as a weighted sum of negative exponential terms. Fix and Neyman also discuss estimation procedures for fitting the parameters in their model.

Marshall and Goldhamer, [4], presented several discrete Markov chain models as a framework for the handling of data in connection with the epidemiology of mental disease. Their object was to characterize the age distributions of the mentally ill population. The states which figured in their analysis were the following:

1. Alive, sane
2. Alive, insane (mild) unhospitalized
3. Alive, insane (severe) unhospitalized
4. Insane, hospitalized
5. Dead, outside of mental institution.

The authors give a long discussion of their data and estimation procedures. Since their model supposes as the underlying descriptive equations

$$P(n + 1) = A P(n) \quad (2.2)$$

where  $P(n)$  is the vector of state probabilities after  $n$  epochs, the form of the solution is always fixed to be  $P(n) = A^n P(0)$ .

The most recent discussion of the Markov model has been given by Alling, [5], as an aid in interpreting data on pulmonary tuberculosis. Alling's model uses the discrete Markov chain, as might be natural in a situation involving periodic examinations. The model provided excellent agreement with experimental data.

All of the Markov models (with constant transition probabilities) have in them the assumption that the probability density for a stay in a given state is of the form  $\varphi(t) = \lambda \exp(-\lambda t)$  or the discrete analogue. In order to introduce a more general model to describe the same phenomena, a somewhat deeper discussion is required of the way in which time is introduced as a descriptive measure of the disease. Toward this end we note that time can be involved in the history of a disease, either as external or internal time relative to the patient. A strictly Markov model assumes that transitions in the state of a patient depend only on the time external to the patient. As an example, the susceptibility of a person to catching a cold may depend more on the season than when he has last had a cold. On the other hand, the change of state of a person with a cancerous disease will depend more critically on how long he has had the growth than on other external circumstances. It is for the description of diseases which require that internal time be taken into account that the theory of semi-Markov processes is appropriate.

### 3. Elements of the Model

We shall consider a model consisting of two mutually exclusive sets of states A and T in which the patients may find themselves. The state A corresponds to the set of absorbing states and T refers to the transient states. The set A can be void as in the description (to a good approximation) of the cold; it may consist of a single state, as for example death in the description of acute leukemia; or it may consist of two states, cure or death, as in a description of tuberculosis. We will assume stationarity of the processes, in the sense that aging effects will not be taken into account. We further assume the following:

- (a) The duration of stay in any state is a random variable.

Specifically, the probability density for a stay in state i which is followed by a stay in state j will be denoted<sup>3</sup> by  $\varphi_{ij}(t)$  where the  $\varphi_{ij}(t)$  may contain delta function components.

We also define the survival function (tail probability integral)

$$\Phi_{ij}(t) = \int_t^{\infty} \varphi_{ij}(x) dx . \quad (3.1)$$

- (b) The probability of a change from state i to state j in a single step (conditional on leaving i) is  $p_{ij}$  where the  $p_{ij}$  are independent of time.

- (c) The p.d.f.  $\varphi_{ij}(t)$  is assumed to possess moments of any order. The kth moment of  $\varphi_{ij}(t)$  will be denoted by  $m_{ij}(k)$ .

---

<sup>3</sup> It is particularly convenient to have two subscripts on these probability distributions since we may be concerned with the termination of stay in a state by different causes. In the present work, in which we are concerned mainly with an absorbing set of states, it will be found that only unconditional probability densities are really necessary.

In addition to the notation and assumptions introduced above we define

$$\left. \begin{aligned} U_i(t) &= \Pr \{ \text{patient in state } i \text{ at time } t \} \\ \omega_i(t)dt &= \Pr \{ \text{patient leaves state } i \text{ during } (t, t+dt) \} \\ \varphi_i(t) &= \sum_j p_{ij} \varphi_j(t), \quad m_i(k) = \int_0^\infty t^k \varphi_i(t) dt \\ \Phi_i(t) &= \int_t^\infty \varphi_i(x) dx. \end{aligned} \right\} \quad (3.2)$$

Since we also allow for the possibility that an initial occurrence of state  $i$  might have a different p.d.f., define  $\varphi_{ij}^0(t)$  as the p.d.f. of the initial stay in state  $i$  followed by a stay in state  $j$ . Also,  $m_{ij}^0(k)$  will denote the corresponding kth moment.

Matrices or vectors of quantities will be denoted by bold face type; the same symbol being used for the matrix as are used for its components.

Consequently we have

$$\left. \begin{aligned} U(t) &= (U_1(t), U_2(t), \dots, U_n(t)) \\ \omega(t) &= (\omega_1(t), \omega_2(t), \dots, \omega_n(t)) \\ \varphi(t) &= (\varphi_i(t) \delta_{ij}), \quad \varphi^0(t) = (\varphi_i^0(t) \delta_{ij}) \\ M(k) &= (m_i(k) \delta_{ij}), \quad M^0(k) = (m_i^0(k) \delta_{ij}). \end{aligned} \right\} \quad (3.3)$$

The matrix  $P = (p_{ij})$  will be written as

$$P = \begin{matrix} & \begin{matrix} A & T \end{matrix} \\ \begin{matrix} A \\ T \end{matrix} & \begin{pmatrix} I & O \\ Q & \bar{P} \end{pmatrix} \end{matrix} \quad (3.4)$$

where  $\bar{P} = (p_{ij})$  corresponds to states for which  $i, j \in T$  and  $Q = (p_{ij})$  correspond to states for which  $i \in T$  and  $j \in A$ .

The first problem of interest for our model is the calculation of  $U(t)$ . We shall first show that  $U(t)$  is related to  $\omega(t)$ , and then show that  $\omega(t)$  is the solution to a matrix renewal equation. The components of  $U(t)$  satisfy the equation

$$U_i(t) = U_i^0(t) + \sum_{k \in T} \int_0^t \omega_k(\tau) p_{ki} \Phi_i(t - \tau) d\tau \quad (3.5)$$

or, in matrix notation

$$U(t) = U^0(t) + \int_0^t \omega(\tau) \bar{P} \Phi(t - \tau) d\tau. \quad (3.6)$$

The derivation of (3.5) is immediate. If the patient is in state  $i$  at time  $t$ , he is either in that state for the first time, or the last transition took place at some time  $\tau$  to an occurrence of state  $i$  which is still in progress. It can be observed from (3.6) that  $U(t)$  is simply related to  $\omega(t)$  and other known functions. The matrix  $\omega(t)$ , in turn, can be formed as the solution to a matrix renewal equation, which reads, in component form

$$\omega_i(t) = \omega_i^0(t) + \sum_{k \in T} \int_0^t \omega_k(\tau) p_{ki} \varphi_i(t - \tau) d\tau \quad (3.7)$$

where  $\omega_i^0(t)$  can alternately be expressed as

$$\omega_i^0(t) = U_i^{(0)}(0) \varphi_i^0(t) \quad (3.8)$$

and the  $U_i^{(0)}(t)$  are known initial values of the probability of being in state  $i$ . The equivalent matrix representation of (3.7) is

$$\omega(t) = \omega^0(t) + \int_0^t \omega(\tau) \bar{P} \varphi(t - \tau) d\tau \quad (3.9)$$

The derivation of (3.9) is similar to that of (3.5).

Since the fundamental equations for the description of our model are in convolution form, the use of Laplace transforms casts them in algebraic form and facilitates the calculation of moments. The Laplace transform of any function of time will be denoted with an asterisk and an argument  $s$  e.g.

$$\omega^*(s) = \int_0^\infty e^{-st} \omega(t) dt \quad (3.10)$$

where the Laplace transform of a matrix is the same matrix containing as elements the transform of the original elements. With this convention (3.6) and (3.9) yield the results:

$$\omega^*(s) = \omega^{0*}(s) + \omega^*(s) \bar{P} \varphi^*(s) \quad (3.11)$$

$$U^*(s) = U^{0*}(s) + \omega^*(s) \bar{P} \Phi^*(s) \quad (3.12)$$

The first line can be solved for  $\omega^*(s)$  when  $\operatorname{Re}(s) \geq 0$  since  $|I - P\varphi^*(s)| \neq 0$  in the right hand  $s$  plane. To see this, we note first that  $I - P\varphi^*(0) = (\delta_{ij} - \bar{p}_{ij})$ . We further have the condition<sup>4</sup>

$$1 \geq \sum_j \bar{p}_{ij} \quad (3.13)$$

where strict inequality holds for at least one value of  $i$ . Hence  $I - \bar{P}\varphi^*(0)$  has a weakly dominant main diagonal and its determinant therefore differs from zero, [6]. When  $\operatorname{Re}(s) > 0$  we know that  $|\varphi_i^*(s)| \leq 1$ , hence the inequality of (3.13) is strengthened.

The solution to the relations of (3.11) and (3.12) can therefore be written

$$\begin{aligned} \omega^*(s) &= \omega^{0*}(s) [I - \bar{P}\varphi^*(s)]^{-1} \\ U^*(s) &= U^{0*}(s) + \omega^{0*}(s) [I - \bar{P}\varphi^*(s)]^{-1} \bar{P}\Phi^*(s). \end{aligned} \quad (3.14)$$

It can easily be shown, following Feller's proof for the ordinary renewal equation, [7], that the elements in  $\omega(t)$  which are derived by inverting the Laplace transform  $\omega^*(s)$  are all non-negative. If the set  $A$  is void, i.e., there are no absorbing states, then we can use standard Tauberian techniques to derive asymptotic expressions for  $\omega(t)$  and  $U(t)$ .

---

<sup>4</sup> In the set  $A$  is void, similar considerations lead to the same conclusion for  $\operatorname{Re}(s) \geq 0$ .

#### 4. First Passage Times

We now turn to first passage time problems which are of great importance in applications involving, for example, the comparative efficiency of different drugs in ameliorating the course of a chronic disease. In the particular problem which we studied, the treatment of acute leukemia, a fatal end is inevitable and the set  $A$  consists of a single state. It is then plausible to base a test of efficiency of a drug on the amount of time that a patient is kept alive. Another alternative would be to base efficiency on the amount of time that a patient is kept in a state of relative comfort.

The first question that might reasonably be asked is, how long will the patient remain in one of the disease states? Let  $f(t)$  be the probability density for the time to reach some absorbing state. Then we have

$$f(t) = \sum_{i \in T} \sum_{j \in A} \omega_i(t) p_{ij} = \omega(t) Q \quad (4.1)$$

Questions relating to the particular absorbing state in which the patient finally finds himself can be answered by reference to well-known results from the theory of finite Markov chains since these results are independent of duration of stay. For this purpose, let  $H$  be a single absorbing state and  $Q_H$  be the column vector in  $A$  corresponding to state  $H$ . Then the probability that a patient will eventually end in the absorbing state  $H$  is

$$q_H = U^0 (I - \bar{P})^{-1} Q_H. \quad (4.2)$$



When  $A$  consists only of the single state  $H$ , it is easily verified that  $q_H = 1$ <sup>5</sup>. The probability density function for the amount of time spent in the transient states  $T$  conditional on final absorption by  $H$  is

$$f_H(t) = \frac{\omega(t) Q_H}{q_H} \quad (4.3)$$

We now proceed to calculate expressions for the moments by using the value of  $\omega^*(s)$  given in (3.14) as a moment generating function. The  $k$ th moment for the total stay in the set of  $T$  states conditional on absorption by  $H$  is

$$E(t^k) = A_k Q_H / q_H \quad (4.4)$$

where the  $A_k$  are defined recursively by

$$\begin{aligned} A_{k+1} (I - \bar{P}) &= U^0 M^0 (k+1) + \binom{k+1}{1} A_k \bar{P} M(1) \\ &+ \binom{k+1}{2} A_{k-1} \bar{P} M(2) + \dots + U^0 (I - P)^{-1} M(k+1). \end{aligned} \quad (4.5)$$

---

<sup>5</sup> We are indebted to Dr. Joan Rosenblatt for pointing out that if  $A$  is a single state then  $Q$  can be written in alternative form as

$$Q = (I - \bar{P}) \begin{pmatrix} 1 \\ \vdots \\ 1 \end{pmatrix}$$

From this form it is easy to see that  $\int_0^\infty f(t) dt = 1$ , since  $\omega^*(0) = U^{(0)} (I - \bar{P})^{-1}$ .

The first two of the  $A_k$  are explicitly

$$\begin{aligned}
 A_1 &= U^0 \{ M^0(1) + (I - \bar{P})^{-1} \bar{P} M(1) \} (I - \bar{P})^{-1} \\
 A_2 &= U^0 \{ M^0(2) + (I - \bar{P})^{-1} \bar{P} M(2) + \\
 &\quad + 2[M^0(1) + (I - \bar{P})^{-1} \bar{P} M(1)] (I - \bar{P})^{-1} \bar{P} M(1) \} (I - \bar{P})^{-1} \quad (4.6)
 \end{aligned}$$

Formal expressions for the higher values of the subscript are easily derived in this fashion. When the set  $A$  consists only of  $H$ , there is some simplification afforded by using the expression for  $Q$  in terms of  $(I - \bar{P})$ , since this term will cancel  $(I - \bar{P})^{-1}$  which post-multiplies the expression for  $A_k$ .

## 5. Distribution of Time Spent in a Single State

5.1 The p.d.f.  $\varphi_{ij}(t) = \varphi_i(t)$ . One further distribution that has potential application in drug comparisons is the distribution of time spent in a single one of the transient states. We shall first find the distribution of the time spent in the particular transient state  $i (i \in T)$ , on the assumption that  $\varphi_{ij}(t) = \varphi_i(t)$ . Let the partition of the transition matrix  $P$  be

$$P = \begin{array}{ccc|c} & A & i & T-j \\ \left[ \begin{array}{ccc} I & O & O \\ \delta & O & \beta \\ \gamma & \alpha & \Pi \end{array} \right] & A & i & T-i \end{array} \quad (5.1)$$

Thus  $\alpha$  is a vector which contains all the information about transitions from  $T - 1$  to  $i$ ;  $\beta$  is a vector of transition probabilities from  $i$  to  $T - 1$ ; etc. Note that the probability of a state beginning in  $T - 1$  will lead to state  $i$  before it leads to an absorbing state is

$$R = \alpha + \Pi \alpha + \Pi^2 \alpha + \dots = (I - \Pi)^{-1} \alpha. \quad (5.2)$$

Let  $h_{ii}$  be the probability that a patient once in state  $i$  will return to state  $i$  before reaching an absorbing state. Further, let  $h_{ji}$  be the probability that a patient in state  $j$  will reach state  $i$  before reaching an absorbing state. We shall find the Laplace transform for the time spent in state  $i$ , starting from state  $j$ ,

$$\psi_j^*(s) = \sum_{n=0}^{\infty} P_j(n) \nu_n^*(s) \quad (5.3)$$

where  $P_j(n)$  is the probability that the patient is in state  $i$  exactly  $n$  times beginning from an occurrence of state  $j$ , and  $\nu_n^*(s)$  is the Laplace transform of the probability density for the total time spent in occurrences of state  $i$ .

The parameters  $h_{ii}$  and  $h_{ji}$  are given in the notation of (5.1) by

$$\begin{aligned} h_{ii} &= \beta \Pi (I - \Pi)^{-1} \alpha = \beta \Pi R \\ h_{ji} &= (R)_j = [(I - \Pi)^{-1} \alpha]_j \end{aligned} \quad (5.4)$$

The derivation of  $h_{ji}$  follows immediately from the definition of  $R$ ; the derivation of  $h_{ii}$  follows from the expansion

$$h_{ii} = \sum_R \sum_{j \in T-i} \{ \beta_j (\Pi)_{jk} \alpha_k + \beta_j (\Pi^2)_{jk} \alpha_k + \dots \} . \quad (5.5)$$

The patient starts in state  $i$ , makes a transition to state  $j$  with probability  $\beta_j$ ; remains in  $T - i$  one or more epochs ending in state  $k$  with probability  $[\Pi (I - \Pi)^{-1}]_{jk}$ , and finally returns to  $i$  with probability  $\alpha_k$ .

The probability that there are exactly  $n$  occurrences of state  $i$  is

$$P_j(n) = \begin{cases} h_{ii}^{n-1} (1 - h_{ii}), & j = i \\ 1 - h_{ji}, & j \neq i, \quad n = 0 \\ h_{ji} h_{ii}^{n-1} (1 - h_{ii}), & j \neq i, \quad n \geq 1 \end{cases} . \quad (5.6)$$

Hence, we find for  $\Psi_j^*(s)$  the expression

$$\Psi_j^*(s) = \frac{(1 - h_{ii}) \varphi_i^{0*}(s) \delta_{ij}}{1 - h_{ii} \varphi_i^*(s)} + \left\{ 1 - h_{ji} + \frac{h_{ji} (1 - h_{ii}) \varphi_i^*(s)}{1 - h_{ii} \varphi_i^*(s)} \right\} (1 - \delta_{ij}). \quad (5.7)$$

If we denote the  $k$ th moment of the total sojourn time in state  $i$  by a patient who starts out in state  $j$  by  $\mu_{ji}(k)$  we find for the first two moments

$$\begin{aligned} \mu_{ji}(1) &= [m_i^0(1) + \frac{h_{ii} m_i(1)}{1 - h_{ii}}] \delta_{ij} + \frac{h_{ji} (1 - \delta_{ij}) m_i(1)}{1 - h_{ii}} \\ \mu_{ji}(2) &= [m_i^0(2) + \frac{2m_i^0(1) m_i(1) h_{ii} + h_{ii} m_i(1)}{1 - h_{ii}} + \\ &\quad + \frac{2h_{ii}^2 [m_i(1)]^2}{(1 - h_{ii})^2}] \delta_{ij} + h_{ji} (1 - \delta_{ij}) \left[ \frac{m_i(2)}{1 - h_{ii}} + 2h_{ii} \frac{[m_i(1)]^2}{(1 - h_{ii})^2} \right] . \end{aligned} \quad (5.8)$$

5.2 General Case. The more general case for determining the distribution of total time spent in the transient state  $i$  when the sojourn time distribution  $\varphi_{ij}(t)$  depends on the state immediately following is quite complicated. In this section we will only indicate the nature of the results. Let  $\zeta_i(t)dt$  denote the probability density for the event that the patient is in state  $i$  ( $i \in T$ ) for an amount of time in  $(t, t+dt)$ . Also define  $W$  to be the vector of probabilities that a chain of states starting from some state  $j \in T - i$  will end in absorption without leading to state  $i$ . The expression for  $W$  is seen to be

$$W = \gamma + \Pi \gamma + \Pi^2 \gamma + \dots = (I - \Pi)^{-1} \gamma \quad (5.9)$$

on the assumption that  $A$  consists of a single state.

Then the Laplace transform of  $\zeta_i(t)$  can be written as the sum of two components

$$\zeta_i^*(s) = \zeta_{i1}^*(s) + \zeta_{i2}^*(s) \quad (5.10)$$

where

$$\begin{aligned} \zeta_{i1}^*(s) &= U_i^0(0) \left\{ [\lambda^{0*}(s) W]_i + \delta \lambda_{iA}^{0*}(s) + \frac{[\lambda^{0*}(s) R]_i [\lambda^*(s) W]_i}{1 - [\lambda^*(s) R]_i} \right\} \\ \zeta_{i2}^*(s) &= \frac{(\sum_{j \neq i} U_j^0(0) R_j) [\lambda^*(s) W]_i}{1 - [\lambda^*(s) R]_i} \end{aligned} \quad (5.11)$$

and where

$$\left. \begin{aligned} \lambda^*(s) &= (p_{ij} \varphi_{ij}^*(s)), \quad \lambda^{0*}(s) = (p_{ij} \varphi_{ij}^{0*}(s)), \quad i, j \in T \\ \lambda_{iA}^{0*}(s) &= (p_{ij} \varphi_{iA}^{0*}(s)), \quad \varphi_{iA}^*(s) = \sum_{j \in A} p_{ij} \varphi_{ij}^{0*}(s) \end{aligned} \right\} \quad (5.11a)$$

The moments of the duration of time spent in state  $i$  are obtained by successive differentiation of  $\zeta_i^*(s)$ . Defining the vectors

$$\Omega_k^0 = (p_{ij} m_{ij}^0(k)), \quad \Omega_k = (p_{ij} m_{ij}(k)) \quad (5.12)$$

the first two moments can be written

$$\begin{aligned} E(t_i) &= U_i^0 \left[ \Omega_1^0 W + \delta m_{iA}(1) + \frac{(\Omega_1^0 R)(\beta W) + (\beta R)(\Omega_1 W)}{1 - \beta R} \right. \\ &\quad \left. + \frac{(\beta R)(\beta W)(\Omega_1 R)}{(1 - \beta R)^2} \right] + \left( \sum_{j \neq i} U_j^0 R_j \right) \left[ \frac{\Omega_1 W}{1 - \beta R} + \frac{(\beta W)(\Omega_1 R)}{(1 - \beta R)^2} \right], \\ E(t_i^2) &= U_i^0 \left[ \Omega_2^0 W + \delta m_{iA}(2) + \frac{(\Omega_1^0 R)(\beta W) + 2(\Omega_1^0 R)(\Omega_1 W) + (\beta R)(\Omega_2 W)}{1 - \beta R} \right. \\ &\quad + \frac{1}{(1 - \beta R)^2} [2(\Omega_1^0 R)(\beta W)(\Omega_1 R) + 2(\beta R)(\Omega_1 R)(\Omega_1 W) + (\beta R)(\beta W)(\Omega_2 R)] \\ &\quad + \frac{2}{(1 - \beta R)^3} (\beta R)(\beta W)(\Omega_1 R)^2 \left. \right] + \left( \sum_{j \neq i} U_j^0 R_j \right) \left[ \frac{\Omega_1 W}{1 - \beta R} \right. \\ &\quad \left. + \frac{2(\Omega_1 W)(\Omega_1 R) + (\beta W)(\Omega_2 R)}{(1 - \beta R)^2} + \frac{2(\beta W)(\Omega_1 R)^2}{(1 - \beta R)^3} \right] \quad (5.13) \end{aligned}$$

## 6. Application of the Model to Patients With Acute Leukemia

6.1 Outline of the six state model. A large scale set of clinical trials was conducted by Acute Leukemia Group B (Frei et al. [8]) on patients having acute-leukemia. In this section we will apply our semi-Markov model to a portion of the data from these clinical trials.

The data considered here are from the records of 54 patients with lymphocytic leukemia. All patients entered these clinical trials while in a state of relapse. The patients received therapy and either continued in relapse, expired, or had a partial or complete remission. The stay in a remissive state is only temporary and the patients ultimately suffer a relapse. Additional therapy is given and the patients either expire or again reach a remissive state. Ultimately all patients expire as the effect of the therapy is only transitory. Among the patients in the study discussed here, no more than two remissions were attained by any patient. The therapy is described by Frei et al, [8], and essentially consists of two phases. Phase I consists of initially giving the patients methotrexate (MTX). Phase II consists of therapy with 6-mercaptopurine (6-MP). Phase I was continued for all patients in the initial relapse state. If at the end of six weeks, the patients had not responded to the treatment (and were still alive), the treatment was terminated. A lapse of two weeks was allowed after which the patients were placed in Phase II. The particular phase which the patient was receiving was discontinued when the patient relapsed from a remission state. The patient was then placed in the alternate phase.

In our application we will be mainly interested in the distribution of the time to failure. Further, since a remissive state is always followed by a relapse, we will combine the sojourn time in a relapse state with that in the remissive state which immediately preceded it. Also the data seem to indicate different characteristics for the sojourn times in the various states. These are a function of the number of times the patient has been in the state.

With these characteristics of the process in mind, we define the six states:

- $S_0$ : failure (death)
- $S_1$ : initial relapse state (condition of patient on entering study)
- $S_2$ : first partial remission (also includes subsequent relapse)
- $S_3$ : second partial remission (includes subsequent relapse)
- $S_4$ : first complete remission (includes subsequent relapse)
- $S_5$ : second complete remission (includes subsequent relapse)

The communication between states is summarized in Figure 1.

Some typical case histories are:

<u>Patient number</u>	<u>Condition</u>	<u>Duration of Stay in State (weeks)</u>
14	initial relapse failure	12
88	initial relapse first partial remission relapse failure	2 34 10
284	initial relapse first complete remission relapse second partial remission relapse failure	4 13 24 40 8



Applying equation (3.14) with five transient states results (after some algebra) in the Laplace transforms for  $\omega^*(s)$  and  $U^*(s)$ ; i. e.

$$\begin{aligned}
 \omega_1^*(s) &= \varphi_1^*(s) \\
 \omega_2^*(s) &= p_{12} \varphi_1^*(s) \varphi_2^*(s) \\
 \omega_3^*(s) &= p_{12} p_{23} \varphi_1^*(s) \varphi_2^*(s) \varphi_3^*(s) + p_{14} p_{43} \varphi_1^*(s) \varphi_3^*(s) \varphi_4^*(s) \\
 \omega_4^*(s) &= p_{14} \varphi_1^*(s) \varphi_4^*(s) \\
 \omega_5^*(s) &= p_{12} p_{25} \varphi_1^*(s) \varphi_2^*(s) \varphi_5^*(s) + p_{14} p_{45} \varphi_1^*(s) \varphi_4^*(s) \varphi_5^*(s) \\
 U_1^*(s) &= \Phi_1^*(s) \\
 U_2^*(s) &= p_{12} \varphi_1^*(s) \Phi_2^*(s) \\
 U_3^*(s) &= p_{12} p_{23} \varphi_1^*(s) \varphi_2^*(s) \Phi_3^*(s) + p_{14} p_{43} \varphi_1^*(s) \varphi_4^*(s) \Phi_3^*(s) \\
 U_4^*(s) &= p_{14} \varphi_1^*(s) \Phi_4^*(s) \\
 U_5^*(s) &= p_{12} p_{25} \varphi_1^*(s) \varphi_2^*(s) \Phi_5^*(s) + p_{14} p_{45} \varphi_1^*(s) \varphi_4^*(s) \Phi_5^*(s)
 \end{aligned} \tag{6.1}$$

The probability density function  $f_0(t)$  of the time to reach  $S_0$  from  $S_1$  can now be obtained from (4.3) with  $Q_H = (p_{10}, p_{20}, p_{30}, p_{40}, p_{50})$ .

Hence we have

$$f_0(t) = \sum_{i=1}^5 \omega_i(t) p_{i0} \quad (6.2)$$

where  $\omega_i(t)$  can be obtained by taking the inverse Laplace transform of  $\omega_i^*(s)$ .

The moments for the time to reach the failure state can now be immediately written down by using equation (4.4)  $E(t^k) = A_k Q_0$  with the recursive relation (4.5). The results for the mean and variance are

$$\begin{aligned} E(t) &= m_1(1) + p_{12} m_2(1) + m_3(1) [p_{12} p_{23} + p_{14} p_{43}] + p_{14} m_4 \\ &\quad + m_5 [p_{12} p_{25} + p_{14} p_{45}] \\ \sigma^2(t) &= \sigma_1^2 + p_{12} \sigma_2^2 + a \sigma_3^2 + p_{14} \sigma_4^2 + b \sigma_5^2 + p_{12} (1 - p_{12}) m_2^2(1) \\ &\quad + a(1 - a) m_3^2(1) + p_{14} (1 - p_{14}) m_4^2(1) + b(1 - b) m_5^2(1) \\ &\quad + 2 \left\{ m_2(1) m_3(1) [p_{12} (p_{23} - a)] - m_2(1) m_4(1) p_{12} p_{14} \right. \\ &\quad + m_2(1) m_5(1) [p_{12} (p_{25} - b)] + m_3(1) m_4(1) [p_{14} (p_{43} - a)] \\ &\quad \left. - m_3(1) m_5(1) ab + m_4(1) m_5(1) [p_{14} (p_{45} - b)] \right\} \quad (6.3) \end{aligned}$$

where  $\sigma_i^2 = m_i(2) - m_i(1)^2$ , and

$$a = p_{12} p_{23} + p_{14} p_{43}, \quad b = p_{12} p_{25} + p_{14} p_{45}.$$

In applying the data to the model it is of interest to study the distribution to reach the failure state, conditional on the patient also reaching a remission state. Denoting the p.d.f. of this conditional distribution by  $g_0(t)$ , we have

$$g_0(t) = \frac{f_0(t) - \omega_1(t) p_{10}}{1 - p_{10}} = \sum_{i=2}^5 \omega_i(t) p_{i0} / (1 - p_{10}) \quad (6.4)$$

The mean and variance of the time to reach the failure state (6.3) is similarly modified by replacing  $p_{10}$  by  $p_{10}/(1 - p_{10})$ .

Another complication in applying the model is that the treatment given the patients depended on the length of time they remained in the initial relapse state. Those patients who stayed in the initial relapse state for a period of eight weeks or less were in Phase I, whereas those who remained for more than six weeks received Phase I therapy followed by Phase II therapy.

6.2 Estimation of parameters. It remains to estimate the parameters in the model. These are the  $(p_{ij})$  and the sojourn time distribution for the various states. The relative frequencies observed in the clinical trials were used as estimates of the  $p_{ij}$ . The numerical results are:

$$P_I = \begin{array}{c} \begin{array}{cccccc} S_0 & S_1 & S_2 & S_3 & S_4 & S_5 \end{array} \\ \left[ \begin{array}{c|cccccc} 1 & 0 & 0 & 0 & 0 & 0 \\ \hline 5/31 & 0 & 10/31 & 0 & 16/31 & 0 \\ 5/10 & 0 & 0 & 3/10 & 0 & 2/10 \\ 1 & 0 & 0 & 0 & 0 & 0 \\ 9/16 & 0 & 0 & 4/16 & 0 & 3/16 \\ 1 & 0 & 0 & 0 & 0 & 0 \end{array} \right] \begin{array}{c} S_0 \\ S_1 \\ S_2 \\ S_3 \\ S_4 \\ S_5 \end{array} \end{array}$$

$$P_{II} = \begin{array}{c} \begin{array}{cccccc} S_0 & S_1 & S_2 & S_3 & S_4 & S_5 \end{array} \\ \left[ \begin{array}{c|cccccc} 1 & 0 & 0 & 0 & 0 & 0 \\ \hline 8/23 & 0 & 4/23 & 0 & 11/23 & 0 \\ 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 9/11 & 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 & 0 \end{array} \right] \begin{array}{c} S_0 \\ S_1 \\ S_2 \\ S_3 \\ S_4 \\ S_5 \end{array} \end{array}$$

The subscripts I and II refer to those patients that either were in Phase I or II when they left the initial relapse state.

An investigation of the distribution of sojourn times within the various transient states showed that these distributions could very well be approximated

by gamma distributions; i. e.

$$\varphi(t) = \frac{\lambda (\lambda t)^{a-1}}{\Gamma(a)} e^{-\lambda t}, \quad a > 0. \quad (6.5)$$

The parameters  $\{a, \lambda\}$  were estimated by the method of maximum likelihood with the aid of the very convenient tables of Wilk, Gnanadesikan, and Huyett, [9] .

Due to the small number of patients in group II, we decided to combine the sojourn time data for groups I and II. Table I summarizes the results of these calculations.

TABLE I: Maximum Likelihood Estimates of the Parameters of the Gamma Distribution

State	$\hat{a}$	$\hat{\lambda}$	n (sample size)
$S_2$ (first P.R.)	2.33	0.101	14
$S_3$ (second P.R.)	2.87	.122	7
$S_4$ (first C.R.)	4.71	.132	27
$S_5$ (second C.R.)	15.54	.463	7

Table II summarizes the sample means and variances for the two groups.

TABLE II: Sample Means and Variances (Patients reaching remission only)

	$\hat{m}(1)$		$\hat{\sigma}^2$		n (sample size)	
	I	II	I	II	I	II
$S_1$ (initial relapse)	4.2	12.6	1.7	11.7	26	15
$S_2$ (first P. R.)	19.2	33.0	124	301	10	4
$S_3$ (second P. R.)	33.0	--	215	--	7	0
$S_4$ (first C. R.)	38.6	31.4	435	260	16	11
$S_5$ (second C. R.)	34.8	31.0	98	128	5	2

The initial relapse state sojourn time distribution (conditional on reaching remission) for groups I and II are both truncated distributions. The distribution for group I is truncated at the upper tail at eight weeks; whereas group II is truncated at the left tail at eight weeks. Since the observations are in discrete time units (weeks) this truncation problem can be handled by taking these sojourn time distributions to be discrete distributions. The estimates of the point probabilities used were the observed relative frequencies. These relative frequencies are:

Weeks I (II)		1(9)	2(10)	3(11)	4(12)	5(13)	6(14)	7(15)	(18)	(22)
I	P =	0	2/26	6/26	8/26	5/26	4/26	1/26	0	0
II	P =	2/15	2/15	1/15	5/15	2/15	1/15	0	1/15	1/15

The weeks in parentheses refer to the times for group II.

A check on our model can be obtained by comparing the sample mean and variance of the time to reach failure with the theoretical formulae given in (6.3).

The numerical results (conditional on going to remission) are:

	I		II	
	Data	Model	Data	Model
Mean	48.4	49.7	48.5	48.6
Variance	515	525	358	408

The agreement is very good.

We now turn our attention to estimating the distribution of the time to reach the failure state (conditional on reaching a remissive state). The probability density function can be written explicitly from (6.2) and (6.4); i. e.

$$\begin{aligned}
 g_0(t) = (1 - p_{10})^{-1} & \left\{ p_{20} p_{12} [\varphi_1 * \varphi_2] + p_{30} p_{12} p_{23} [\varphi_1 * \varphi_2 * \varphi_3] \right. \\
 & + p_{40} p_{14} [\varphi_1 * \varphi_4] + p_{30} p_{14} p_{43} [\varphi_1 * \varphi_3 * \varphi_4] \\
 & \left. + p_{50} p_{12} p_{25} [\varphi_1 * \varphi_2 * \varphi_5] + p_{50} p_{14} p_{45} [\varphi_1 * \varphi_4 * \varphi_5] \right\} \quad (6.6)
 \end{aligned}$$

(The notation  $\varphi_1 * \varphi_2$  denotes the convolution of  $\varphi_1(t)$  and  $\varphi_2(t)$  etc.). Note that  $g_0(t)$  is made up of a mixture of distributions which involve convolutions of gamma distributions. We approximated the convolution of gamma distributions by a gamma distribution having the same first two moments. It was felt that a more sophisticated approximation was not necessary.

Figure II compares the cumulative distributions obtained from the model with the empirical cumulative distribution for both groups I and II. Both the empirical and theoretical distributions for II have been adjusted by using 8 weeks as the origin. The agreement of the model with the data is excellent for group I. However the agreement at the lower tail for group II is not good. This probably is due to the nature of the data where at the early stages of phase II treatment, there are undoubtedly some effects from phase I still present. Also on Figure II, the failure time distribution for patients not going into remission is given for comparison.

#### 7. Acknowledgement.

The authors would like to express their sincere appreciation to Dr. Edmund Gehan for obtaining the acute leukemia data and for many helpful discussions about this data.



## BIBLIOGRAPHY

1. Pyke, R. , Markov Renewal Processes with Finitely Many States,  
Ann. Math. Stat. 32, 1243 (1961).
2. Weiss, G. H. , On a Semi-Markovian Process with a Particular Application to Reliability, NAVORD Report, 4351, U.S. Naval Ordnance Laboratory, White Oak, Md.
3. Fix, E. , Neyman, J. , A Simple Stochastic Model of Recovery, Relapse, and Loss of Patients, Human Biology, 23, 205 (1951).
4. Marshall, A. W. , Goldhamer, H. , An Application of Markov Processes to the Study of the Epidemiology of Mental Disease , J. Am. Stat. Assoc. 50, 99 (1955).
5. Alling, D. , The After-History of Pulmonary Tuberculosis , Biometrics, 14, 527 (1958).
6. Taussky-Todd, O. , A Recurring Theorem on Determinants, Ann. Math. Monthly, 56, 672 (1954).
7. Feller, W. , On the Integral Equation of Renewal Theory, Ann. Math. Stat. 12, 243 (1941).
8. Frei, E. , et al. , Studies of Sequential and Combination Antimetabolite Theory in Acute Leukemia: 6- Mercaptopurine and Methotrexate, Blood, 18, 431 (1961).
9. Wilk, M. , Gnanadesikan, Huyett, M. J. , Estimation of Parameters of the Gamma Distribution using Order Statistics, Biometrika, 49 525 (1962).

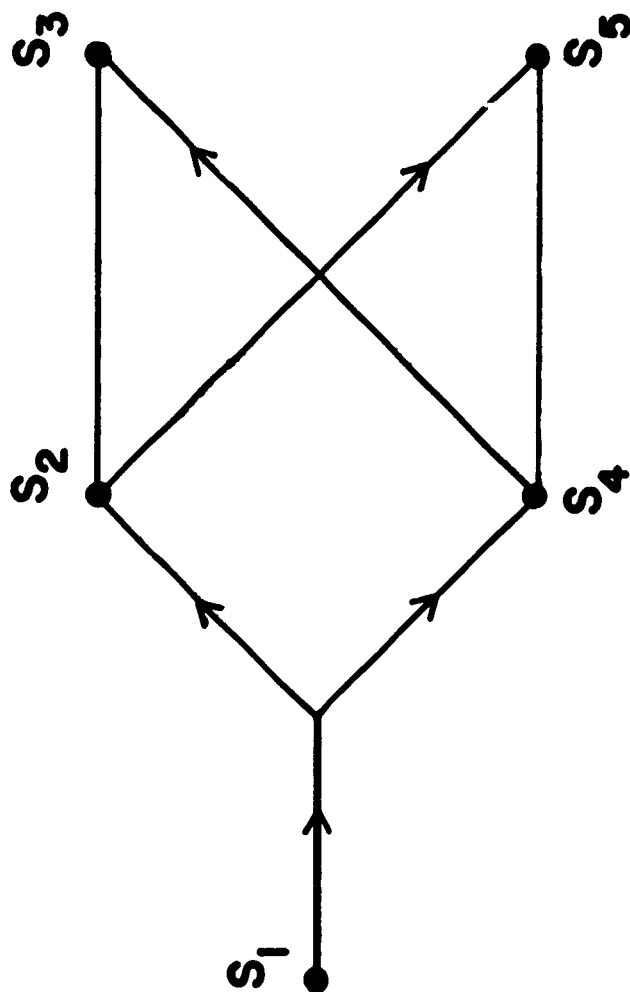


Figure 1: State diagram for communications between states. All states communicate with  $S_0$ .

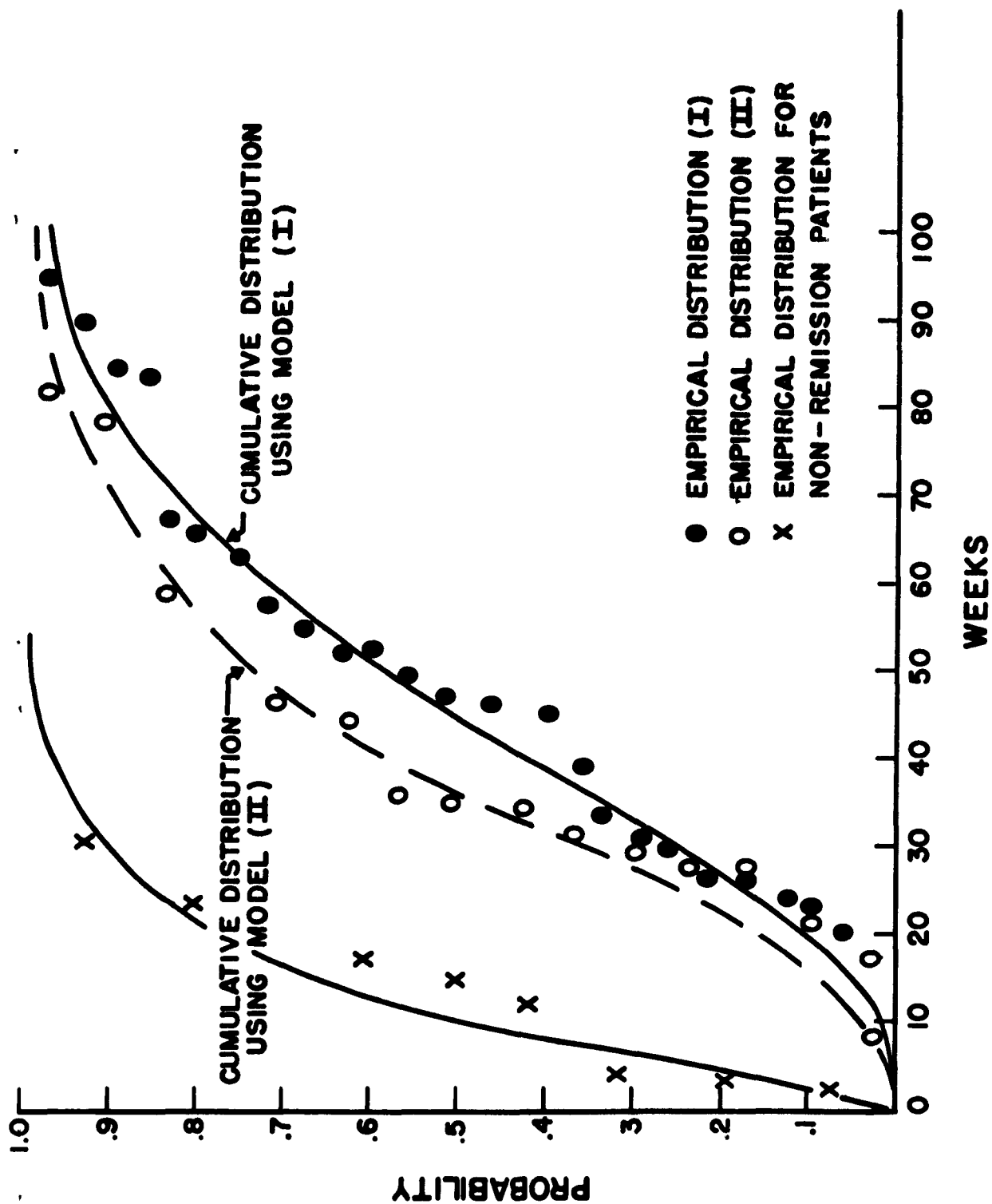


Figure 2: Distribution function for the time to failure for patients in Phases I and II, as well as those who never left a state of relapse.